12 www.rialto.com/favism/english/index.mv (accessed 9 Jan 2007).
13 **Gilsanz F**, Vega MA, Gomez-Castillo E, *et al*. Fetal anaemia due to pyruvate kinase deficiency. *Arch Dis Child* 1993;**69**:523–4.
14 **Zanella A**, Bianchi P. Red cell pyruvate kinase deficiency: from genetics to clinical manifestations. *Bailliere's Best Pract Res Clin Haematol* 2000;**13**:57–81.
15 **Schneider AS**. Triosephosphate isomerase deficiency: historical perspectives and molecular aspects. *Bailliere's Best Pract Res Clin Haematol* 2000;**13**:119–40.
16 **Davies SC**, Cronin E, Gill M, *et al*. Screening for sickle cell disease and thalassaemia: a systematic review with supplementary research. *Health Technol Assess*. 2000;4: iii–v, 1–99).
17 **Higgs DR**. Alpha-thalassaemia. *Bailliere's Clin Haematol* 1993;**6**:117–50.
18 **Chik KW**, Shing MM, Li CK, *et al*. Treatment of hemoglobin Bart's hydrops with bone marrow transplantation. *J Pediatr* 1998;**132**:1039–42.
19 **Sohan K**, Billington M, Pamphilon D, *et al*. Normal growth and development following in utero diagnosis and treatment of homozygous alpha-thalassaemia. *BJOG* 2002;**109**:1308–10.
20 **Lee-Potter JP**, Deacon-Smith RA, Simpkiss MJ, *et al*. A new cause of hemolytic anemia in the newborn. *J Clin Pathol* 1975;**28**:317–20.
21 **Howard H**, Martlew V, McFadyen I, *et al*. Consequences for fetus and neonate of maternal red cell alloimmunisation. *Arch Dis Child Fetal Neonatal Ed* 1998;**78**:F62–6.
22 **Stockman JA**, de Alarcon PA. Overview of the state of the art of Rh disease: history, current clinical management, and recent progress. *J Pediatr Hematol Oncol* 2001;**23**:385–93.
23 **Thompson J**. Haemolytic disease of the newborn: the new NICE guidelines. *J Fam Health Care* 2002;**12**:133–6.
24 **Vaughan JI**, Manning M, Warwick RM, *et al*. Inhibition of erythroid progenitor cells by anti-Kell antibodies in fetal alloimmune anemia. *N Engl J Med* 1998;**338**:798–803.
25 **Bennett PR**, Le Van Kim C, Colin Y, *et al*. Prenatal determination of fetal RhD type by DNA amplification. *N Engl J Med*, 1993 26, **329**:607–10.
26 **Al-Mufti R**, Howard C, Overton T, *et al*. Detection of fetal messenger ribonucleic acid in maternal blood to determine fetal RhD status as a strategy for noninvasive prenatal diagnosis. *Am J Obstet Gynecol* 1998;**179**:210–4.
27 **Bianchi DW**, Avent ND, Costa JM, *et al*. Noninvasive prenatal diagnosis of fetal Rhesus D: ready for Prime(r) Time. *Obstet Gynecol* 2005;**106**:841–4.
28 **Urbaniak SJ**, Greiss MA. RhD haemolytic disease of the fetus and the newborn. *Blood Rev* 2000;**14**:44–61.
29 **Harkness UF**, Spinnato JA. Prevention and management of RhD isoimmunization. *Clin Perinatol* 2004;**31**:721–42.
30 **Yaseen H**, Khalaf M, Rashid N, *et al*. Does prophylactic phototherapy prevent hyperbilirubinemia in neonates with ABO incompatibility and positive Coombs' test? *J Perinatol* 2005;**25**:590–4.
31 **Newman TB**, Liljestrand, PJeremy RJ, et al. Outcomes among newborns with total serum bilirubin levels of 25 mg per deciliter or more. *N Engl J Med*, 2006;4, **354**:1889–900.
32 **van Kamp IL**, Klumper FJ, Meerman RH, *et al*. Treatment of fetal anemia due to red-cell alloimmunization with intrauterine transfusions in the Netherlands, 1988-1999. *Acta Obstet Gynecol Scand* 2004;**83**:731–7.
33 **Murray NA**, Roberts IA. Neonatal transfusion practice. *Arch Dis Child Fetal Neonatal Ed* 2004;**89**:F101–7.
34 **Dinesh D**. Review of positive direct antiglobulin tests found on cord blood sampling. *J Paediatr Child Health* 2005;**41**:504–7.
35 **Cortey A**, Brossard Y. [Adverse effects and patient information]. *J Gynecol Obstet Biol Reprod (Paris)* 2006;**35**(1 Suppl):1S112–1S118.
36 **Cremer RJ**, Perryman PW, Richards DH. Influence of light on the hyperbilirubinaemia of infants. *Lancet*, 1958 24, **1**(7030):1094–7.
37 **Vreman HJ**, Wong RJ, Stevenson DK. Phototherapy: current methods and future directions. *Semin Perinatol* 2004;**28**:326–33.
38 **Hart G**, Cameron R. The importance of irradiance and area in neonatal phototherapy. *Arch Dis Child Fetal Neonatal Ed* 2005;**90**:F437–40.
39 **Vreman HJ**, Wong RJ, Stevenson DK, *et al*. Light-emitting diodes: a novel light source for phototherapy. *Pediatr Res* 1998;**44**:804–9.
40 **Seidman DS**, Moise J, Ergaz Z, *et al*. A prospective randomized controlled study of phototherapy using blue and blue-green light-emitting devices, and conventional halogen-quartz phototherapy. *J Perinatol* 2003;**23**:123–7.
41 **Thaithumyanon P**, Visutiratmanee C. Double phototherapy in jaundiced term infants with hemolysis. *J Med Assoc Thai* 2002;**85**:1176–81.
42 **McDonagh AF**. Phototherapy: from ancient Egypt to the new millennium. *J Perinatol* 2001;**21**(Suppl 1):S7–S12.
43 **Miqdad AM**, Abdelbasit OB, Shaheed MM, *et al*. Intravenous immunoglobulin G (IVIG) therapy for significant hyperbilirubinemia in ABO hemolytic disease of the newborn. *J Matern Fetal Neonatal Med* 2004;**16**:163–6.
44 **Mukhopadhyay K**, Murki S, Narang A, *et al*. Intravenous immunoglobulins in rhesus hemolytic disease. *Indian J Pediatr* 2003;**70**:697–9.
45 **Alpay F**, Sarici SU, Okutan V, *et al*. High-dose intravenous immunoglobulin therapy in neonatal immune haemolytic jaundice. *Acta Paediatr* 1999;**88**:216–9.
46 **Dagoglu T**, Ovali F, Samanci N, *et al*. High-dose intravenous immunoglobulin therapy for rhesus haemolytic disease. *J Int Med Res* 1995;**23**:264–71.
47 **Voto LS**, Sexer H, Ferreiro G, *et al*. Neonatal administration of high–dose intravenous immunoglobulin in rhesus hemolytic disease. *J Perinat Med* 1995;**23**:443–51.
48 **Rubo J**, Albrecht K, Lasch P, *et al*. High-dose intravenous immune globulin therapy for hyperbilirubinemia caused by Rh hemolytic disease. *J Pediatr* 1992;**121**:93–7.
49 **Alcock GS**, Liley H. Immunoglobulin infusion for isoimmune haemolytic jaundice in neonates. *Cochrane Database Syst Rev* 2002;**3**:CD003313.
50 **Gottstein R**, Cooke RW. Systematic review of intravenous immunoglobulin in haemolytic disease of the newborn. *Arch Dis Child Fetal Neonatal Ed* 2003;**88**:F6–10.
51 **Hayakawa F**, Imada K, Towatari M, *et al*. Life-threatening human parvovirus B19 infection transmitted by intravenous immune globulin. *Br J Haematol* 2002;**118**:1187–9.
52 **Quinti I**, Pierdominici M, Marziali M, *et al*. European surveillance of immunoglobulin safety--results of initial survey of 1243 patients with primary immunodeficiencies in 16 countries. *Clin Immunol* 2002;**104**:231–6.
53 **Dennery PA**. Metalloporphyrins for the treatment of neonatal jaundice. *Curr Opin Pediatr* 2005;**17**:167–9.

Preterm labour

The management of preterm labour

Jayanta Chatterjee, Joanna Gullam, Manu Vatish, Steve Thornton

Preterm labour is the onset of regular uterine contractions associated with progressive cervical change between viability and 37 completed weeks of gestation. The incidence is between 5% and 10% in most developed nations. In the US, the incidence has increased from 9% to 12% in the past two decades. Preterm delivery can be associated with immediate and long-term neonatal complications. Long-term morbidity includes cerebral palsy, neurodevelopmental delay and chronic lung disease. The neonatal outcome is dependent on the gestational age at delivery and associated features such as infection. The lower the gestational age, the higher the risk of mortality and morbidity. The management of preterm labour involves identification of high-risk women, prevention and treatment.

IDENTIFICATION OF AND PREVENTION IN WOMEN AT RISK

The identification of women at high risk of preterm delivery remains a major challenge. Scoring systems based on socioeconomic status, obstetric or medical history and antenatal events in the index pregnancy have shown a suboptimal correlation with subsequent preterm birth.[1] This is primarily because the single greatest risk factor is a history of preterm labour, so delivery cannot be reliably predicted in the first pregnancy. The risk of preterm delivery after one and two previous preterm deliveries has been given as 15% and 41%, respectively[1]; however, such figures are difficult to apply to individuals as the risk is dependent on the cause and the gestational age of the previous preterm delivery.

Investigations such as fetal fibronectin or cervical ultrasound can be used to identify women at high risk. A positive swab for vaginal fetal fibronectin taken in the late second or early third trimester increases the likelihood of delivery before 34 weeks by a factor of 4.[2] Likewise, a negative swab reduces the likelihood of delivery to 0.78. Such results from

meta-analysis include women both at high risk and at low risk. A recent study[3] in which testing at 24 weeks was restricted to women at high risk has shown a likelihood ratio of 11.8 and 0.48 for a positive test and a negative test, respectively. Thus, fetal fibronectin is a helpful indicator for subsequent preterm delivery.

There is also good evidence that measurement of cervical length can be used as a predictor. In a study of 2567 asymptomatic women with singleton pregnancies, cervical length measurement was taken at 23 weeks gestation.[4] The rate of preterm delivery below 32 weeks was 1%, 4% and 78% for cervical lengths of >25 mm, <15 mm and <5 mm, respectively. Cervical length also predicts preterm delivery in high-risk women. A likelihood ratio of 4.7 has been reported for preterm delivery at <35 weeks with a cervical length <25 mm in women with a previous cone biopsy.[5] Furthermore, there is evidence that a short cervix is associated with earlier rather than late preterm birth[6] and that the mean cervical length is shorter in women with a history of preterm delivery.[7]

Although fetal fibronectin and cervical length provide indicators of the risk of preterm delivery, a subsequent change in management (see below) has not been shown to improve the outcome. For this reason, routine identification of high-risk women by fibronectin or ultrasound screening is not usually undertaken outside clinical trials. In clinical practice, the determination of risk, therefore, tends to be based on obstetric history and management restricted to the identification and treatment of bacterial vaginosis, using progesterone or cervical cerclage.

Screening and treatment of bacterial vaginosis

Bacterial vaginosis is a polymicrobial condition associated with preterm delivery. Although there is little doubt that women with bacterial vaginosis are more likely to deliver preterm, there is considerable debate regarding whether low-risk women should be screened and treated. A large study[8] of low-risk women with bacterial vaginosis found no significant difference in the rate of preterm delivery in those randomised to receive metronidazole or placebo (12.2% and 12.5%, respectively). However, subsequent discussion has highlighted several methodological considerations such as whether the results would have been different if women had been treated at an earlier gestational age. The results of this trial are in contrast with two smaller studies[9 10] that used clindamycin rather than metronidazole as the active agent. Both of these have shown a reduction in preterm delivery associated with treatment.

In contrast with the screening and treatment of low-risk women, the data are more consistent for those at high risk. In a study of 624 high-risk women,[11] treatment of bacterial vaginosis with metronidazole and erythromycin was associated with a marked reduction in preterm delivery from 49% to 31%. Such data are supported by another study[12] that showed that metronidazole reduced the rate of preterm rupture of the membranes and delivery. A recent Cochrane[13] review on 5300 women from 13 trials concluded that only in high-risk women did antibiotics reduce the risk of preterm prelabour rupture of the membranes and low birth weight. However, there was no overall effect on the incidence of preterm delivery.

Given the evidence available, it seems reasonable to screen women for bacterial vaginosis if they are at high but not at low risk of preterm delivery. High risk essentially means a history of or symptoms of bacterial vaginosis. Treatment should be given to those in whom a diagnosis is made. Systemic metronidazole or topical clindamycin has been the mainstay of treatment for many years. However, recent evidence[14] suggests that administration of metronidazole in women with a positive fetal fibronectin may be associated with a worsening of pregnancy outcome, so the authors currently favour topical clindamycin as the first-choice treatment.

Progesterone

Progesterone promotes pregnancy and uterine quiescence. There is extensive evidence that withdrawal is associated with the onset of labour in many species, although such a process has not been known to occur in women. Nevertheless, administration of the progesterone antagonist mifepristone can initiate delivery. This, and other data, supports the concept that progesterone maintains pregnancy in women. Administration of progesterone for the prevention of preterm labour is therefore logical. There has recently been renewed interest in the administration of progesterone prophylaxis to women at high risk. The possibility that progesterone may be effective was initially investigated >20 years ago, although meta-analyses gave conflicting results.[15 16] In view of this, a further analysis was done by Keirse,[17] which suggested that 17α-hydroxyprogesterone caproate (17OHP), but not other progestagenic agents, may be associated with a reduction in preterm delivery in high-risk women. The meta-analysis results were largely ignored until two recent randomised controlled trials of progesterone were published.[18 19] The larger trial[18] randomised 459 women to receive intramuscular 17OHP or placebo (in a ratio of 2:1) until 37 weeks gestation. There was a significant reduction in preterm deliveries below 37, 35 and 32 weeks. There was also a reduction in the rates of birth weight <2500 kg, intraventricular haemorrhage, need for supplemental oxygen and necrotising enterocolitis, although these were not the primary outcomes. This trial provides good evidence that 17OHP administration can reduce preterm deliveries in high-risk women, although the high rate of preterm delivery in the placebo group and a number of methodological considerations have led to extensive discussion about the results. Given that 17OHP was identified as the effective progestational agent in the Keirse meta-analysis,[17] it is perhaps surprising that natural vaginal progesterone has also been reported to considerably reduce the risk of early delivery in high-risk women.[19] Furthermore, recent data[20] suggest that medroxy-progesterone but not progesterone prevents inflammation-induced parturition and intrauterine fetal demise. The clinical studies are supported by two recent meta-analyses that suggest that both 17OHP and natural vaginal progesterone reduce the risk of preterm delivery in high-risk women.[21 22] Thus, there is good evidence that progestagenic agents reduce the risk of preterm labour in some high-risk women, but evidence for improved neonatal outcome is presently inconclusive. Hence, given the methodological concerns alluded to above, it is reasonable to await confirmation of safety and improved neonatal outcome associated with progesterone before routine administration.

Cervical cerclage

Elective cerclage may be indicated when there is a congenital or acquired weakness in the cervix that increases the risk of late miscarriage or preterm delivery. Historically, the diagnosis of cervical weakness has been made on clinical symptoms, usually painless dilatation of the cervix or spontaneous rupture of the membranes before the onset of labour in the late second or early third trimester. Unfortunately, there is little consensus on which women will benefit from cerclage and definitive evidence is often lacking. The largest study to investigate the effects of cerclage in high-risk women (based on medical history) was the Medical Research Council/Royal College of Obstetricians and Gynaecologists (RCOG) trial[23] reported in 1993. This trial showed that there were fewer preterm

deliveries at <33 weeks in women who had cerclage and concluded that this trend is indicated in women with a history of ⩾3 mid-trimester losses. The method of this study has, however, been questioned. Women were recruited only if the obstetrician was unsure whether to place a stitch. This means that if the obstetrician considered that cerclage would be helpful, the woman would not have been recruited. Only those women in whom the benefits were more borderline were randomised. This means that those women with the greatest potential to benefit may not have been included. Despite the difficulties in interpreting this trial, it remains the largest and most influential guide to clinical practice. Attempts to clarify the situation by meta-analysis of reported trials have not been particularly helpful as there is considerable heterogeneity in reported outcomes[24 25] and the Medical Research Council/RCOG trial is the major contributor to the data.

Recently, after the publication of a number of supporting trials, there has been a trend for cerclage in women identified to have a short cervix on midtrimester ultrasound.[26 27] However, differing trial methods make the studies difficult to compare, and others[28] have not confirmed these promising results perhaps owing to a difference in the patient population. It has been suggested that cerclage may be helpful if the cervix is short in the subgroup whose history suggests cervical incompetence. Cerclage may not be helpful in those women who have a short cervix without a history of incompetence. Given this uncertainty, To *et al*[29] screened more than 47 000 women at the routine second trimester scan. The 233 women with a cervical length of ⩽15 mm were allocated to cerclage or expectant management. There were no differences in the rate of delivery at <33 weeks or in other outcomes between the two groups. Thus, on current evidence there seems to be little justification for screening low-risk women by ultrasound as cerclage does not improve the outcome in those with a short cervix. However, meta-analysis supports the above data, in that there may be some value in screening (and insertion of cerclage if the cervix is short) in women with a history of cervical incompetence.[30] Our practice is not to screen low-risk women by ultrasound, to insert a cervical stitch in women with an appropriate (albeit subjective) history, and to confine ultrasound scanning to women who decline elective cerclage. We do not scan the cervix after cerclage as there is no current evidence that additional procedures will improve the outcome.

The efficacy of different types of cerclage has not been tested rigorously. Each has its advocates. Transvaginal techniques (McDonald or Shirodkar) differ in the anatomical level of the cerclage. The McDonald procedure places a purse-string stitch in the stroma of the ectocervix at the level of reflection of the vaginal fornices. The Shirodkar suture requires an incision in the vaginal mucosa, reflection of the pubo-cervical fascia at the level of the internal os which the suture to be placed at the level of the cardinal ligaments. It has been suggested that the Shirodkar suture maintains a functional internal os which may be important for efficacy, and that the buried knot removes a potential focus of infection. However, logically, if cerclage is effective, it is unlikely to be due to the cerclage preventing cervical dilation by mechanical means. Preterm delivery or preterm prelabour rupture of the membranes may be prevented by lengthening the cervix, thereby reducing the risk of ascending infection. If the latter is true, there is no reason to suppose that the Shirodkar procedure is more effective as long as the cervical length is ⩾2 cm after cerclage. Given that the Shirodkar suture may be more traumatic, many obstetricians will continue to favour the technically easier McDonald procedure until additional evidence is available. It also seems reasonable to reserve the more invasive trans-abdominal procedure for the small proportion of women in whom the vaginal procedure is inappropriate.

TREATMENT

Management of preterm labour should be directed towards establishing the cause, ensuring delivery under optimal conditions, and consideration of the pros and cons of delaying delivery to increase gestational age. In practice, this means that women admitted in threatened preterm labour should be appropriately assessed to determine the optimal time for delivery. The presence of fetal compromise or intrauterine infection can hinder prolonging the pregnancy, whereas early gestational age and uncomplicated preterm labour with intact membranes can mitigate a delay in delivery. The decision should be based on a risk–benefit analysis for each individual. The main pharmacological considerations are whether to administer antibiotics, steroids or tocolytics.

Antibiotics

Preterm delivery is often associated with evidence of chorioamnionitis, and the earlier the gestational age at delivery, the greater the risk. However, it is often not clear whether infection or inflammation is the cause or an effect of preterm delivery. In women with uncomplicated preterm labour without ruptured membranes, the ORACLE trial failed to show improved neonatal outcome[31] with antibiotic administration. As this trial recruited over 6000 women, it dominates the subsequent meta-analysis[32] and the conclusions from the latter are therefore similar. At present, antibiotics cannot be justified for the treatment of preterm labour in the absence of prelabour rupture of the membranes. However, both ORACLE[31 33] and the subsequent meta-analysis[32] suggest that, if rupture of the membranes occurs preterm before the onset of labour, administration of erythromycin is associated with prolongation of pregnancy and improved neonatal outcome. As an adverse effect of augmentin on neonatal necrotising enterocolitis was noted, erythromycin seems a logical first-choice antibiotic.

Steroids

There is good evidence suggesting that antenatal steroids should be given to mothers who have threatened preterm labour to reduce the incidence of neonatal respiratory distress syndrome, intraventricular haemorrhage and perinatal death.[34] Discussion is ongoing about whether they should be given at <24 weeks or >34 weeks and, although the RCOG recommend up to 36 weeks,[35] most babies born at >34 weeks survive without problems. The benefits of the time interval between administration and delivery being between 24 h and 7 days have been shown,[34] but there is probably some advantage even outside these times. Although an improved outcome has not been shown in multiple pregnancies, the current consensus is that steroids should be given. Most clinicians give betamethasone, as a large observational study showed a reduced incidence of periventricular leucomalacia compared with use of dexamethasone.[36] Results of a randomised, controlled trial of dexamethasone and betamethasone are awaited. Comparison of oral and intramuscular administration has shown that, although there was no difference in the incidence of respiratory distress syndrom, the incidence of neonatal sepsis and intraventricular haemorrhage were greater in the neonates of mothers receiving oral steroids.[37] Current recommendations are therefore to give intramuscular betamethasone. A single course of maternal steroids is associated with improved neonatal outcome,[38] and detrimental effects have not been identified in follow-up studies for up to 20 years.[39] However, there are major concerns regarding the effect of repeated courses on neurological development, neonatal or

maternal infection, birth weight, adrenal suppression, maternal osteoporosis and impaired glucose tolerance.[40 41] Thus, a single course of betamethasone should be given to almost all mothers in threatened preterm labour unless contraindicated or delivery is imminent.

Tocolysis

Most authorities believe that tocolysis is likely to be beneficial in uncomplicated preterm labour, although this has not been shown in clinical trials. Meta-analysis of tocolysis compared with placebo or no treatment has shown a delay in delivery and maternal side effects associated with tocolysis but without improved perinatal outcome.[42] The reason for the maternal side effects is concerning and could be patient selection (those with the potential for an adverse outcome may not have been identified). The time gained was not used to undertake measures that would improve the outcome (eg the rate of steroid administration was low at around 36%). Patients were included at a gestational age at which a delay in delivery was unlikely to provide a measurable improvement in outcome. There are insufficient large studies available to show an effect on the outcome. Such reports have led to the publication of guidelines that do not mandate tocolysis to delay delivery in uncomplicated preterm labour.[43] Despite such guidance, most authorities administer tocolytics either to delay delivery long enough to allow steroids to have an effect or to instigate other measures that are likely to improve the outcome, such as transfer to a unit with neonatal special care facilities. Assuming that tocolysis is administered, the question then becomes which drug should be used. Guidelines from the RCOG[43] support the use of the calcium channel blocker nifedipine or the oxytocin antagonist atosiban.

Nifedipine

Nifedipine prevents the calcium influx critical for myometrial cell contraction. It is not specific for uterine smooth muscle and is also commonly used to relax vascular smooth muscle for the treatment of hypertension. Although there are neither placebo nor double-blind controlled trials of nifedipine for the treatment of preterm labour, fewer maternal side effects and improved neonatal outcome have been reported in women given nifedipine rather than ritodrine.[44] Meta-analysis of the clinical trials[45] that compare nifedipine with any other tocolytic (usually ritodrine) also provides evidence for a delay in delivery, reduction in deliveries at <34 weeks and improved neonatal outcome. Nevertheless, the individual trials included in the analysis have been extensively discussed as: (1) high comparator concentrations of ritodrine might have been used, leading to patient withdrawal due to side effects; (2) none were double blind; (3) many were small; or (4) patients might have been given ritodrine before the study and rescue tocolysis used.

The issue of rescue is important as, if preterm labour continues, a second drug may be administered. This means that outcomes cannot be assessed readily—for example, normally, if preterm labour is not suppressed by the experimental drug, there will be an increase in the rate of delivery. However, if for example, indomethacin (an effective tocolytic) was given as rescue, this could prevent delivery or cause side effects, making interpretation of maternal and perinatal outcomes meaningless. Thus, although the clinical trials and meta-analyses of nifedipine suggest that the drug is effective and may improve the outcome, the results should be interpreted with an understanding of the methodological limitations of the included trials. Recently there have been reports of serious maternal side effects associated with administration of calcium channel blockers,[46 47] although a causative link cannot be assumed. Despite the quality of the available evidence, reports of improved outcomes have led many clinicians to administer nifedipine as their first-line treatment for uncomplicated preterm labour.

Atosiban

Atosiban is an analogue of oxytocin that inhibits activity at oxytocin and vasopressin (V_{1a}) receptors. Given reports of increased oxytocin at the onset of labour,[48] it represents a logical treatment for preterm uterine contractions. Large placebo-controlled and double-blind comparator trials have been performed to investigate the effectiveness of atosiban for the treatment of preterm labour.[49] However, as with the nifedipine trials, rescue tocolysis has often been used, mandating the composite outcome of ''delivery or use of alternative tocolytic''. Some secondary outcomes cannot therefore be accurately assessed for the reason discussed above.

A large placebo-controlled, double-blind trial of atosiban[50] analysed 249 women in threatened preterm labour in each of the placebo and atosiban groups. There was no marked difference in the primary outcome of time to delivery or therapeutic failure, although the number of women undelivered and not requiring an alternative tocolytic was significantly higher at 24 h, 48 h and 7 days in women who received atosiban. This trial recruited more women at very early gestational ages to receive atosiban and this is likely to have caused an increase in fetal/infant death in the atosiban group. An adverse effect of atosiban on this outcome has not been observed in other trials.

There have been three large studies comparing atosiban with β sympathomimetics,[51–53] and these have also been published as a pooled comparison.[54] The pooled study analysed data on 362 women who received atosiban and 379 who were given β sympathomimetics. The primary outcomes were effectiveness and safety. The results showed that there was no difference in the proportion of women who delivered after 2 or 7 days, or in neonatal or infant outcomes. There were, however, marked differences in maternal side effects and the rate of drug discontinuation due to adverse effects, both of which favoured atosiban. The composite outcome of efficacy and tolerability (therapeutic failure) was considerably better in the atosiban group at 2 and 7 days for singleton pregnancies. Taken together, these studies show that atosiban is as effective as β sympathomimetics, without the maternal side effects.

Large clinical trials to compare atosiban with nifedipine are awaited. There have been two smaller trials of 80[55] and 63 women each,[56] randomised to receive nifedipine or atosiban. Neither drug was shown to be significantly superior, albeit that the trials may have been underpowered.

Meta-analyses[57] of the atosiban data have been undertaken to compare outcomes with placebo or comparator and, in an indirect comparison, have been reported for nifedipine.[58] These failed to show improved tocolytic efficacy or infant outcomes with atosiban compared with placebo or comparator. Nevertheless, the validity of the conclusions has been questioned, partly because of the difficulties in comparing outcomes in trials with rescue treatment. Overall, given that large placebo and comparator trials have been undertaken, atosiban is licensed in Europe, and there are few concerns regarding maternal safety, the data have been taken by many clinicians to justify the cost of atosiban and use it as the first-line treatment for threatened preterm labour.

CONCLUSION

Preterm labour is a multifactorial condition associated with a high risk of morbidity and mortality, particularly at early gestational ages. Prevention is directed towards identification of women at risk and comprises screening and treatment for bacterial vaginosis, insertion of cerclage in

appropriate women, and consideration of progesterone prophylaxis. The treatment of established preterm labour should be directed towards identifying those women in whom a delay in delivery is likely to be beneficial and those in whom it may be deleterious in terms of neonatal or infant outcome. Although there is little hard evidence that tocolysis improves the outcome for the baby, most obstetricians treat threatened uncomplicated preterm labour in order to administer steroids or transfer the mother to an appropriate hospital. Current guidelines support treatment with nifedipine or atosiban, both of which have their advocates. Our recommendations are to treat threatened, uncomplicated preterm labour with an oxytocin antagonist to delay delivery for steroid administration or transfer to an appropriate unit for delivery. Given that a single course of steroids should be given, we believe there is no indication for subsequent retreatment.

Arch Dis Child Fetal Neonatal Ed 2007;**92**:F88–F93.
doi: 10.1136/adc.2005.082289

Authors' affiliations
Jayanta Chatterjee, Department of Obstetrics and Gynaecology, Warford General Hospital, Watford, UK
Joanna Gullam, Manu Vatish, Steve Thornton, University of Warwick, Coventry, Warwickshire, UK

Correspondence to: J Chatterjee, Department of Obstetrics and Gynaecology, Watford General Hospital, Vicarage Road, Watford, WD18 0HB, UK; jaychatt@yahoo.com

Accepted 17 July 2006

Competing interests: None declared.

REFERENCES

1 **Mercer BM**, Goldenberg RL, Das A, *et al.* The preterm prediction study: a clinical risk assessment system. *Am J Obstet Gynecol* 1996;**174**:1885–93.
2 **Honest H**, Bachmann LM, Gupta JK, *et al.* Accuracy of cervicovaginal fetal fibronectin in predicting the risk of spontaneous preterm birth: systematic review. *BMJ* 2002;**325**:301–11.
3 **Shennan A**, Jones G, Hawken J, *et al.* Fetal fibronectin test predicts delivery before 30 weeks of gestation in high risk women, but increases anxiety. *Br J Obstet Gynecol* 2005;**112**:293–98.
4 **Heath VC**, Souka AP, Erasmus I. Cervical length at 23 weeks of gestation: prediction of spontaneous preterm delivery. *Ultrasound Obstet Gynecol* 1998;**12**:312–17.
5 **Berghella V**, Pereira L, Gariepy A, *et al.* Prior cone biopsy: prediction of preterm birth by cervical ultrasound—an observational study. *Am J Obstet Gynecol* 2004;**191**:1393–97.
6 **Owen J**, Yost N, Berghella V, *et al.* Can shortened mid-trimester cervical length predict early spontaneous preterm birth? An observational study. *Am J Obstet Gynecol* 2004;**191**:298–303.
7 **de Carvalho MH**, Bittar RE, Brizot ML, *et al.* Prediction of preterm delivery in the second trimester. *Obstet Gynecol* 2005;**105**:532–6.
8 **Carey JC**, Klebanoff MA, Hauth JC, *et al.* Metronidazole to prevent preterm delivery in pregnant women with asymptomatic bacterial vaginosis. *N Engl J Med* 2000;**342**:534–40.
9 **Ugwumadu A**, Manyonda I, Reid F, *et al.* Effect of early oral clindamycin on late miscarriage and preterm delivery in asymptomatic women with abnormal vaginal flora and bacterial vaginosis: a randomised controlled trial. *Lancet* 2003;**361**:983–8.
10 **Lamont RF**, Duncan SL, Mandal D, *et al.* Intravaginal clindamycin to reduce preterm birth in women with abnormal genital tract flora. *Obstet Gynecol* 2003;**101**:516–22.
11 **Hauth JC**, Goldenberg RL, Andrews WW, *et al.* Reduced incidence of preterm delivery with metronidazole and erythromycin in women with bacterial vaginosis. *N Engl J Med* 1995;**333**:1732–6.
12 **Morales WJ**, Schorr S, Albritton J. Effect of metronidazole in patients with preterm birth in preceding pregnancy and bacterial vaginosis: a placebo-controlled, double-blind study. *Am J Obstet Gynecol* 1994;**171**:345–7.
13 **Mc Donald H**, Brocklehurst P, Parsons J, *et al.* Antibiotics for treating bacterial vaginosis in pregnancy. *Cochrane Database Syst Rev* 2003;(2):CD000262.
14 **Shennan A**, Crawshaw S, Briley A, *et al.* A randomised controlled trial of metronidazole for the prevention of preterm birth in women positive for cervicovaginal fetal fibronectin: the PREMET study. *Br J Obstet Gynaecol* 2006;**113**:65–74.
15 **Daya S**. Efficacy of progesterone support for pregnancy in women with recurrent miscarriage: a meta-analysis of controlled trials. *Br J Obstet Gynaecol* 1989;**96**:275–80.
16 **Goldstein P**, Berrier J, Rosen S, *et al.* A meta-analysis of randomized trials of progestational agents in pregnancy. *Br J Obstet Gynaecol* 1989;**96**:265–74.
17 **Keirse MJ**. Progesterone administration in pregnancy may prevent delivery. *Br J Obstet Gynaecol* 1990;**97**:149–54.
18 **Meis PJ**, Klebanoff M, Thom E, *et al.* Prevention of recurrent preterm delivery by 17 alpha-hydroxyprogesterone caproate. *N Engl J Med* 2003;**348**:2379–85.
19 **da Fonseca EB**, Bittar RE, Carvalho MH, *et al.* Prophylactic administration of progesterone by vaginal suppository to reduce the incidence of spontaneous preterm birth in women at increased risk: a randomised, placebo-controlled double-blind study. *Am J Obstet Gynecol* 2003;**1888**:419–24.
20 **Elovitz M**, Wang Z. Medroxyprogesterone acetate, but not progesterone, protects against inflammation-induced parturition and intrauterine fetal demise. *Am J Obstet Gynecol* 2004;**190**:693–701.
21 **Sanchez-Ramos L**, Kaumitz AM, Delke I. Progestational agents to prevent preterm birth: a meta-analysis of randomized controlled trials. *Obstet Gynecol* 2005;**105**:273–79.
22 **Dodd JM**, Crowther CA, Cincotta R, *et al.* Progesterone supplementation for prevention of preterm birth: a systematic review and meta-analysis. *Acta Obstet Gynecol Scand* 2005;**84**:526–33.
23 **MRC/RCOG Working Party on Cervical Cerclage**. Final report of the Medical Research Council/Royal College of Obstetricians and Gynaecologists-multicentre randomised trial of cervical cerclage. *Br J Obstet Gynaecol* 1993;**100**:516–23.
24 **Drakeley AJ**, Roberts D, Alfirevic Z, *et al.* Cervical cerclage for prevention of preterm birth: meta-analysis of randomized trials. *Obstet Gynecol* 2003;**102**:621–7.
25 **Belej-Rak T**, Okun N, Windrim R, *et al.* Effectiveness of cervical cerclage for a sonographically shortened cervix: a systemic review and meta-analysis. *Am J Obstet Gynecol* 2003;**189**:1679–87.
26 **Heath VC**, Souka AP, Erasmus I, *et al.* Cervical length at 23 weeks of gestation: the value of Shirodkar suture for the short cervix. *Ultrasound Obstet Gynecol* 1998;**12**:318–22.
27 **Althuisius SM**, Dekker GA, Hummel P, *et al.* Final results of the Cervical Incompetence Prevention Randomized Cerclage Trial (CIPRACT): therapeutic cerclage with bed rest versus bed rest alone. *Am J Obstet Gynecol* 2001;**185**:1106–12.
28 **Rust OA**, Atlas RO, Jones KJ, *et al.* A randomized trial of cerclage versus no cerclage among patients with ultrasonographically detected second-trimester preterm dilatation of the internal os. *Am J Obstet Gynecol* 2000;**183**:830–5.
29 **To MS**, Alfirevic Z, Heath VC, *et al.* Cervical cerclage for the prevention of preterm delivery in women with short cervix: Randomised controlled trial. *Lancet* 2004;**363**:1849–53.
30 **Berghella V**, Odibo AO, To S Meekai, et al. Cerclage for short cervix on Ultra sonography. Meta-analysis of trials using individual patient-level data. *Obstet Gynecol* 2005;**106**:181–9.
31 **Kenyon SL**, Taylor DJ, Tarnow-Mordi W. ORACLE Collaborative group. Broad-spectrum antibiotics for spontaneous preterm labour: The ORACLE I randomized trial, *Lancet* 2001;**357**:979–88.
32 **Kenyon SL**, Taylor DJ, Tarnow-Mordi W. Antibiotics for preterm premature rupture of the membranes. *Cochrane Database Syst Rev* 2001;(4):CD001058.
33 **Kenyon SL**, Taylor DJ, Tarnow-Mordi W. ORACLE Collaborative group. Broad-spectrum antibiotics for spontaneous preterm labour: the ORACLE II randomized trial, *Lancet* 2001;**357**:989–94.
34 **Crowley P**. Prophylactic corticosteroids for preterm birth. *Cochrane Database Syst Rev* 2002;(4):CD000065.
35 **Sinclair JC**. Meta-analysis of randomised controlled trials of antenatal corticosteroid administration for the prevention of respiratory distress syndrome: discussion. *Am J Gynecol* 1995;**173**:335–44.
36 **Baud O**, Foix-L'Helias L, Kaminski M, *et al.* Antenatal glucocorticoid treatment and cystic periventricular leucomalacia in very premature infants. *N Engl J Med* 1999;**341**:1190–6.
37 **Egerman RS**, Mercer BM, Doss JL, *et al.* A randomized controlled trial of oral and intramuscular dexamethasone in the prevention of neonatal respiratory distress syndrome. *Am J Obstet Gynecol* 1998;**179**:11120–3.
38 **Doyle LW**, Ford GW, Richards AL, *et al.* Antenatal corticosteroids and outcome at 14 years of age in children with birth weight of less than 1501 grams. *Pediatrics* 2000;**106**:2.
39 **AB, Haas HS, Koppe JG**. Twenty-year follow-up of antenatal corticosteroid treatment. *Pediatrics* 2000;**105**:77.
40 **French NP**, Hagan R, Evans SF, *et al.* Repeated antenatal corticosteroids: size at birth and subsequent development. *Am J Obstet Gynecol* 1999;**180**:114–21.
41 **Newnham JP**, Moss TJ, Nitsos I, *et al.* Antenatal corticosteroids: the good, the bad and the unknown. *Curr Opin Obstet Gynecol* 2002;**14**:607–12.
42 **Gyetvai K**, Hannah ME, Hodnett ED, *et al.* Tocolysis for preterm labour: a systematic review. *Obstet Gynecol* 1999;**94**:869–77.
43 **Royal College of Obstetricians and Gynaecologists**. Tocolytic drugs for women in preterm labour. *Clinical Guidelines No. 1(B)* 2002.
44 **Papatsonis DN**, Van Geijn HP, Ader HJ, *et al.* Nifedipine and ritodrine in the management of preterm labour: a randomised multi-centre trial. *Obstet Gynecol* 1997;**90**:230–4.
45 **King JF**, Flenady V, Papatsonis DN, *et al.* Calcium channel blockers for inhibiting preterm labour. *Cochrane Database Syst Rev,* 2003.10.1002/14651858.CD002255..
46 **van Veen AJ**, Pelinck MJ, Van Pampus MG, *et al.* Severe hypotension and fetal death due to tocolysis with nifedipine. *Br J Obstet Gynaecol* 2005;**112**:509–510.
47 **Vaast P**, Dubreucq-Fossaert S, Houfflin–Debarge V, *et al.* Acute pulmonary oedema during nicardipine therapy for preterm labour; report of five cases. *Eur J Obstet Gynecol Reprod Biol* 2004;**113**:98–9.
48 **Blanks AM**, Vatish M, Allen MJ, *et al.* Paracrine oxytocin and estradiol demonstrate a spatial increase in human intrauterine tissue with labour. *J Clin Endocrinol Metab* 2003;**88**:3392–400.
49 **Romero R**, Chaiworapongsa T, Goncalves LF. Oxytocin antagonists for tocolysis. In: Critchley H, Bennett P, Thornton S, eds. *Preterm birth.* London: RCOG press, 2004, ISBN1-900364-92-1..
50 **R**, Sibai BM, Sanchez-Ramos L, *et al.* An oxytocin receptor antagonist (atosiban) in the treatment of preterm labour: a randomised, double-blind controlled trial with tocolytic rescue. *Am J Obstet Gynecol* 2004;**182**:1173–83.

51 **Moutquin JM**, Sherman D, Cohen H, *et al*. Double-blind, randomized, controlled trial of atosiban and ritodrine in the treatment of preterm labor: a multicentre effectiveness and safety study. *Am J Obstet Gynecol* 2000;**182**:1191–9.

52 **French/Australian Atosiban Investigators Group**. Treatment of preterm labour with the oxytocin antagonist atosiban: a double-blind, randomised, controlled comparison with salbutamol. *Eur J Obstet Gynecol Reprod Biol* 2001;**98**:177–85.

53 **The European Atosiban Study Group**. The oxytocin antagonist atosiban versus the B-agonist Terbutaline in the treatment of preterm labour. A randomised, double-blind, controlled study. *Acta Obstet Gynecol Scand* 2001;**80**:413–22.

54 **The Worldwide Atosiban versus Beta-agonists Study Group**. Effectiveness and safety of the oxytocin antagonist versus beta-adrenergic agonists in the treatment of preterm labour. *Br J Obstet Gynaecol* 2001;**108**:133–42.

55 **Kashanian M**, Akbarian AR, Soltanzadeh M, *et al*. Atosiban and nifedipine for the treatment of preterm labour. *Int J Gynaecol Obstet* 2005;**91**:10–14.

56 **Al-Omari WR**, Al-Shammaa HB, Al-Tikriti EM, *et al*. Atosiban and nifedipine in acute tocolysis: a comparative study. *Eur J Obstet Gynecol Reprod Biol*, 2006; Epub ahead of print PMID, 16446025.

57 **Papatsonis D**, Flenady V, Cole S, *et al*. Oxytocin receptor antagonists for inhibiting preterm labour. *Cochrane Database Syst Revi*. 2005; (3): CD004452, doi:10.1002/ 14651858.CD004452.pub2..

58 **Coomarasamy A**, Ellen M Knox, Harry Gee, et al. Effectiveness of nifedipine versus atosiban for tocolysis in preterm labour; a meta-analysis with an indirect comparison of randomised trials. *Br J Obstet Gynecol* 2003;**110**:1045–9.